

## Relativity: A Design Principle for Adaptation in Biochemical Systems

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### Abstract

Recent technical advancements in molecular biology enable experimental approaches to seek the existence of design principles that unify the organization of diverse biochemical systems and we can begin to discern a mathematical formalism through which a common design principle can emerge from complexity at biochemical, molecular, cellular, and behavior levels. Weber's law applies to a number of cell signaling processes and gene regulation, as well as perception and recognition at behavior level. The biochemical signaling system obeying Weber's law shows the ability to generate signals for reliable fold changes than absolute changes. This enables to decide the characteristics of space, in such a way that the demand of orthogonality in space can be dealt well with the freedom of the time-axis, i.e. the fundamental physical situation at the core of relativity theory. The concept of relativity leads us to understand fully the integrated behavior of the biochemical sensing systems.

**Keywords:** Adaptation; Michaelis-Menten equation; Relativity; Space-time; Weber's law

### Introduction

Recent technical advancements in molecular biology now enable experimental approaches to seek the existence of design principles that unify the organization of diverse biochemical systems across all organisms. For example, it has been well established that astrocytes express a large variety of G-protein-coupled receptors which mediate the transduction of extracellular signals into intracellular response, and that this calcium signaling is the most common measured readout of astrocyte activity in response to stimulation, such as synaptic activity, neuromodulators diffusing in the extracellular milieu, or exogenous chemical, mechanical or optical stimuli [1,2]. This leads to the notions of a common design principle for the biochemical systems and of the importance of looking for the principle organizing structure and function across the biochemical systems. In these developments we can begin to discern a mathematical formalism through which a common design principle can emerge from complexity at biochemical, molecular, cellular, and behavior levels. Finding the mechanism underlying the principle is more tractable and convincing by using mathematics, which is a bridge between the observable and unobservable worlds.

Mathematical formulation is a way understanding and working in nature, leading contemplation and the most powerful proof of the functional role of the biochemical systems, since biological organisms have similar behavioral objectives to adapt to the same environment, that is, the physical world (the earth), and therefore, the functional requirements on their biological systems are similar. In this study, I will explore a principled question: the fundamental issue of the biological signaling systems shared universally across species, by shedding light on the problem of why and how the biochemical sensing can be possible to adapt organisms to the physical world, whose fundamental characteristic is relativity.

### Relativity in the Physical World

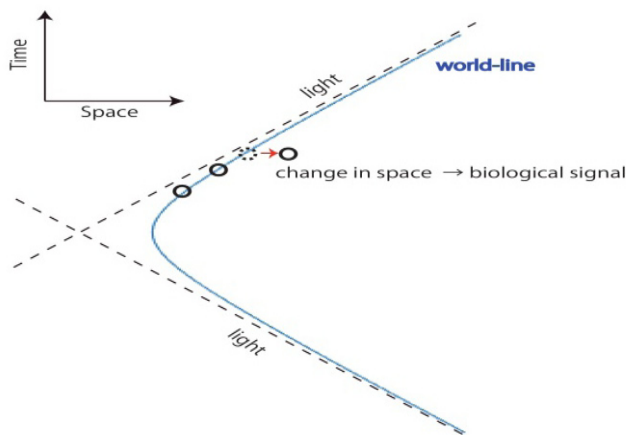
Minkowski [3] presented a proper mathematical understanding of the fundamental physical situation at the core of relativity theory. From the address by Minkowski,

“Space by itself, and time itself, are destined to fade away into mere shadows, and only a kind of union of the two remain an independent reality.”

“Subjects of our perception are always places and times connected. No one has observed a time except at a particular time, or has observed a time except at a particular place”

Minkowski proposed the geometrical (mathematical) structure that yielded direct insight about the underlying substance of the physical universe: the way of describing the unfolding of things across time. He called a space-point at a time-point “world point”, which could be given coordinates  $(x,y,z,t)$  with  $x,y,z$ , representing the rectangular coordinates of space and  $t$  denoting the time. To establish the connection between space and time, the demand of orthogonality in space to do with the perfect freedom of the time-axis towards the upper direction,  $t>0$ , leads to the following formula, taking a positive parameter  $c$ ,  $c^2t^2 - x^2 - y^2 - z^2 = 1$ .

This formula represents the four-dimensional space, where time and 3-dimensional space intermingle, and the Lorentz Geometry of spatial relativity can be well represented; Minkowski geometry, defining the 4-dimensional hyperbolic space, produces the invariance with respect to the Lorentz transformation. Minkowski space-time diagram (see Figure 1), which is a graphical representation of events and sequences of events in spacetime as “seen” by observer at rest, helped Einstein’s quest for general relativity. The moral of relativity is that what is physically objective is not what varies, but rather what remains invariant under such relativistic transformations.



**Figure 1: Minkowski space time diagram.** The cross section of the hyperboloid ( $c^2t^2 - x^2 - y^2 - z^2 = 1$ , with a positive parameter  $c$ ) with the plane of the  $x$ - and  $t$ -axes, i.e., the upper branch of the hyperbola  $c^2t^2 - x^2 = 1$ , in which  $y$  and  $z$  remain unaltered. The whole world is resolved in the world-lines, whose points are unambiguously connected to the parameter  $t$  from  $+\infty$  to  $-\infty$ . The physical laws would find their most perfect expression as mutual relations among these world-lines. The substance existing at any world point can always be considered to be at rest, if time and space are interpreted suitably. By resetting themselves after responding a stimulus and generating signal for a relative change, the interpretation is possible as if the  $x$ -axis of space somehow remains conserved in its position, leading to the proper interpretation of a change in space.

By that formulation, the concept of time is shown to be unambiguously established by natural phenomena, but the concept of space is not altered, because the interpretation is possible as if the  $x$ -,  $y$ -, and  $z$ -axis of space somehow remain conserved in their position. The concept of time is essential for relativity, revealed as follows. The equations of Newtonian mechanics show a twofold invariance having quite separate existences beside each other. First, their form remains unaltered when we subject the underlying spatial coordinate system to any change of position. We look upon the existence of this first group of invariance as a fundamental characteristic of space: at  $t=0$  we can give the  $x,y,z$ -axes an arbitrary rotation about the null-point, corresponding to the homogeneous linear-transformation of the expression  $x^2+y^2+z^2$  in itself. Second, the form of Newtonian mechanics remains unaltered when we change the underlying spatial coordinate system in its state of motion, i.e., when we impress upon it any uniform motion of transformation. But we can never decide from physical considerations whether the space, which is supposed to be at rest, may not finally be in uniform motion: the second group of invariance denotes that - also without changing the expression for the mechanical law- we can substitute  $x,y,z,t$  by  $x-\alpha t, y-\beta t, z-\gamma t, t$  with any constants  $\alpha,\beta,\gamma$ . By the concept of space-time, the  $x,y,z$  manifold (space)  $t=0$ , and its two sides  $t>0$  and  $t<0$  fall apart: any world-point  $O$  as a space-time-null-point consists of two parts with  $O$  as apex, one part having  $t<0$ , fore-side, the other having  $t>0$ , aft-side. Every world-point on the fore-side of  $O$  is necessarily always earlier, and every point on the aft-side of  $O$  is necessarily later than  $O$ . Thus, the fundamental characteristics of space can be decided at  $t=0$ . This has the demand of orthogonality in space to do with the freedom of the time-axis. Note here that in the hyperbolic geometric space, “distance” is defined by natural logarithm.

## Relativity in Biological Signals in Organisms

A common feature in physiological (biological) sensing is Weber’s law, put forward by Weber in 1834 to account for the perception of weight. The law holds for not only the perception of a variety of sensations including weight, sound intensity and pitch, and light intensity, but also for the cognitive judgements such as economic decisions and number estimation [4]. Weber’s law states that ratio between the just noticeable change in a stimulus ( $\Delta S_{\min}$ ) and the background level of the stimulus ( $S_{\text{background}}$ ) is constant,

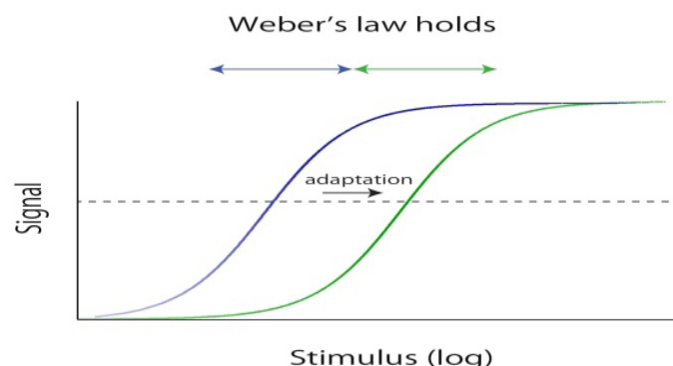
$$\Delta S_{\min} / S_{\text{background}} = k.$$

Thus, in the Weber’s law world, stimuli/things are perceived not in absolute term, but in relative term; their fold change in magnitude relative to the background level of stimulus.

Recently, there is growing evidence showing that Weber’s law also applies to a number of cell signaling processes and gene

regulation (Lee et al., 2014; Cohen-Saidon, et al, 2009; Ferrell, 2009; Goentoro et al., 2009) [5,6,7,8]. Weber's law describes critical and ubiquitous biological behavior, that is, adaptation which refers to the biological system's ability to respond to a change in input stimulus then return to its pre-stimulated output level even when the change in input persists. Adaptation has been considered to enable sensory and other signaling networks to expand the input range that a circuit is able to sense, to more accurately detect changes in the input, and to maintain homeostasis in the presence of perturbations. More importantly, Weber's law satisfies the demand of the biological sensing to do with the relativity of the physical situations, as shown in Figure 1. The biological signaling systems obeying Weber's law shows the ability to reset themselves after responding a stimulus and to generate signals for reliable fold changes than absolute changes. This enables the systems to decide the characteristics of space, in such a way that the demand of orthogonality in space can be suitably dealt with the freedom of the time-axis towards the upper direction. The substance existing at any world point can always be considered to be at rest, if time and space are interpreted suitably. By resetting oneself after responding a stimulus and signaling its relative change, the interpretation is possible as if the x-axis of space somehow remain conserved in its position along the world-line, leading to proper interpretation of a change in space. Thus, a change in space along the world-line evokes a corresponding change in the biological signal, as shown in Figure 1.

Another important point is metric. A response that obeys Weber's law should yield equal increments of output for equal fold increments in stimulus. Thus, a Weber's law response is a straight line on a semilog plot. A hyperbolic or Michaelian response, whose functional form is described in terms of the same as that of the Michaelis-Menten equation, well approximates Weber's law over the middle of its response range, as shown in Figure 2. Enzymes are the basic machinery that makes chemical reactions occur in living cells, and therefore the biological signaling mechanism is the chemical reactions. According to the Michaelis-Menten equation governing the enzyme kinetics, the reaction rate shows the hyperbolic dependence on the substrate in enzyme catalyzed reactions, and then a change in the substrate over time is given by the integrated form of the Michaelis-Menten equation, that is, the logarithmic function. These fundamentals of enzyme kinetics may provide the base for logarithmic transformations. Taking account into the relativity in the physical world, that is, the hyperbolic geometry of space-time, where metric is defined by logarithm, the ubiquitous hyperbolic or Michaelian responses may enable the biochemical systems to describe metrically the unfolding of things/events across hyperbolic structure of space and time, i.e., the physical world.



**Figure 2:** A hyperbolic or Michaelian response, whose functional form is described as the Michaelis-Menten equation, well approximates Weber's law over middle of its response range, yielding equal increments of output for equal fold increments in stimulus. After responding a stimulus (denoted by a blue line), the Michaelian response system resets oneself and generates a signal for a relative change (denoted by a green line).

The idea, introduced by Michaelis and Menten as the Michaelis-Menten equation, have been widely used in different areas of biology, including enzyme kinetics, protein allostery, receptor pharmacology, gene regulation and post-translation modification. The equation is based on the assumption that a part of a system is operating sufficiently fast compared to the rest so that it may be taken to have reached a steady state. An interesting feature of this formula is that it is always rational function in the slow variable, that is, the time-scale separation in enzyme kinetics. The time-scale separation enables to discern the unfolding of substrates across time, by subserving as a time-like vector directed from the null-point towards  $t > 0$ , in Minkowski space-time diagram. The concept of relativity leads us to understand fully the integrated behavior of the biochemical systems.

The author declares no competing interests.

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